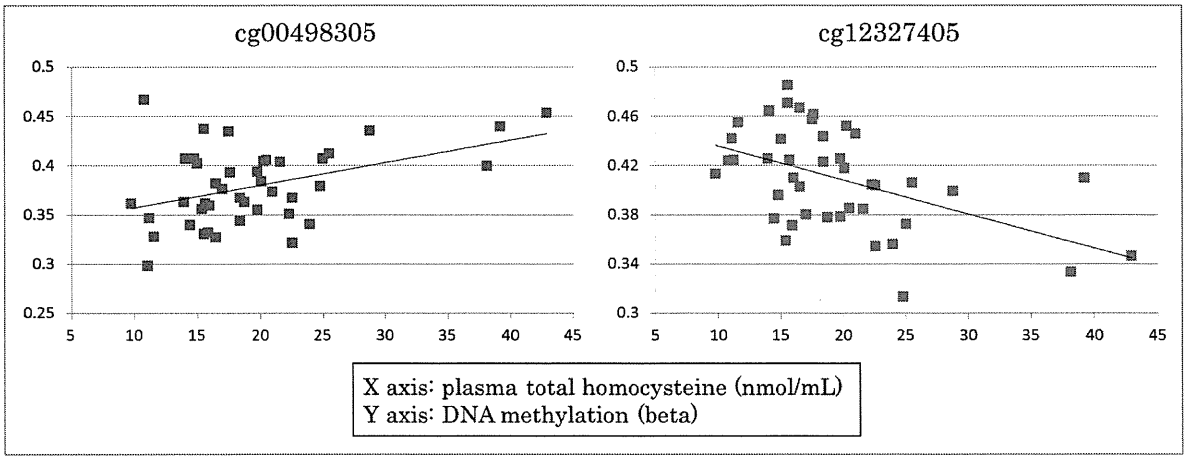

Figure 2. Two CpG sites in the *SLC18A2* (cg00498305) and *GNAL* (cg12327405) genes, which have been implicated in SCZ. A significant positive correlation of plasma total homocysteine with DNA methylation was observed at cg00498305 located in the CGI shore in the promoter region of the *SLC18A2* gene (p = 1.67E−03). A significant negative correlation of plasma total homocysteine with DNA methylation was observed at cg12327405 in the CGI in the promoter region of the *GNAL* gene (p = 2.85E−04). [X-axis: plasma total homocysteine (nmol/mL); Y-axis: DNA methylation (β)].

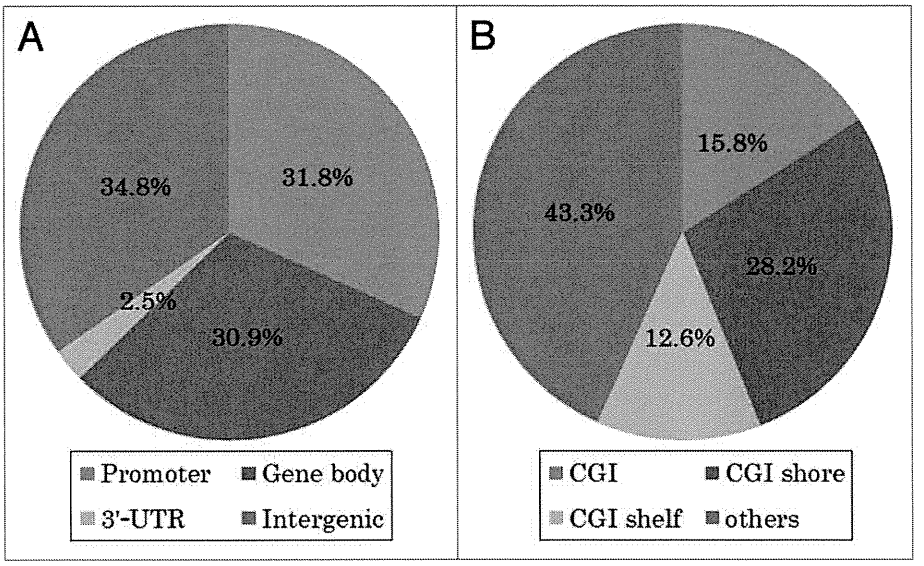

Figure 3. Percentages of 1,338 CpG sites at which plasma total homocysteine and DNA methylation were significantly correlated. (**A**) Of the 1,338 CpG sites, 425 (31.8%) were located in promoter regions, 414 (30.9%) were located in gene bodies and 34 (2.5%) were located in 3'-UTRs. (**B**) Of the 1,338 CpG sites, 212 (15.8%) were located in CGIs, 377 (28.2%) were located in CGI shores and 169 (12.6%) were located in CGI shelves.

DNA methylation methods. Genomic DNA was extracted from peripheral blood using the phenol-chloroform method. Bisulfite conversion of 500 ng of genomic DNA was performed with the EZ DNA methylation kit (Zymo Research). DNA methylation level was assessed with Infinium® HumanMethylation450 BeadChips (Illumina Inc.) according to the manufacturer's instructions. The technical schemes, accuracy, and high reproducibility of this array have been described in previous papers.[56-58] Quantitative measurements of DNA methylation were determined for 485,764 CpG dinucleotides that covered 99% of the RefSeq genes and were distributed across whole gene regions, including promoters, gene bodies, and 3'-UTRs. The arrays also covered 96% of the CGIs from the UCSC database with additional coverage in CGI shores (0–2 kb from CGI) and CGI shelves (2–4 kb from CGI). Detailed information on the contents of the array is available in the Infinium HumanMethylation450 User Guide, HumanMethylation450 manifest (www.illumina.com) and recent papers.[56,58] DNA methylation data was analyzed using the methylation analysis module within the BeadStudio software (Illumina Inc.). DNA methylation status of the CpG sites was calculated as the ratio of the signal from a methylated probe relative to the sum of both methylated and unmethylated probes. This value, known as β, ranges from 0 (completely unmethylated) to 1 (fully methylated). For intra-chip normalization of the probe intensities, colored balance and background corrections in every set of 12 samples from the same chip were performed using internal control probes. X chromosome CpG sites in the CGIs in the *AR* gene as well as the internal control probes were checked to validate the DNA methylation measurements, as in a previous study.[59] Of the 485,764 CpG sites, the loci that have β-values of < 0.1 or > 0.9 were eliminated, as in previous studies.[32,60] The loci that are potentially confoundable with single nucleotide polymorphisms with a minor allele frequency of > 0.1 in the HapMap-JPT population were also removed because DNA methylation is associated with genotypic variants.[61] The final data set includes 164,657 CpG sites.

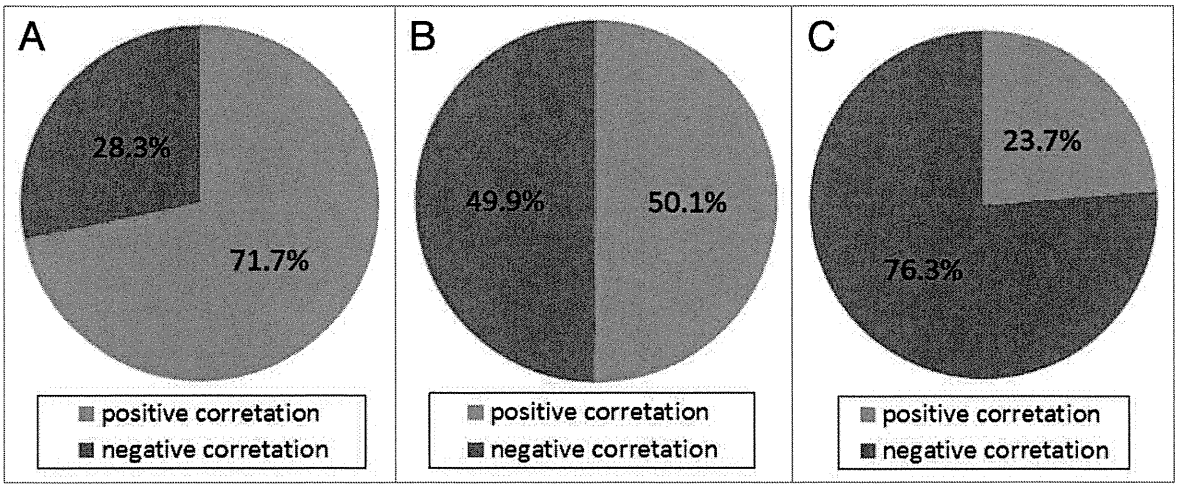

Figure 4. Percentage of CpG sites with positive correlations, located in CGIs, CGI shores and CGI shelves. (**A**) Of the 212 CpG sites located in the CGIs, 152 (71.7%) showed positive correlations between plasma total homocysteine and DNA methylation. (**B**) Of the 377 CpG sites located in the CGI shores, 189 (50.1%) showed positive correlations between plasma total homocysteine and DNA methylation. (**C**) Of the 169 CpG sites located in the CGI shelves, 40 (23.7%) showed positive correlations between plasma total homocysteine and DNA methylation.

Statistical methods. Differences in plasma total homocysteine levels between the two groups were examined using a Mann–Whitney U test. The influences of plasma total homocysteine on DNA methylation was examined with a multiple linear regression analysis adjusted for age and chlorpromazine equivalent dose as potential confounders, after standardizing DNA methylation β and plasma total homocysteine values with Z-scores across the samples.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were dislosed.

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Supplemental Materials

Supplemental materials may be found here:
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ORIGINAL CONTRIBUTION

Season of birth effect on psychotic-like experiences in Japanese adolescents

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Abstract A number of studies have investigated seasonality of birth in schizophrenia. Most of the studies have consistently observed an excess of winter births, often associated with decreased summer births. We postulated that psychotic-like experiences (PLEs), subclinical hallucinatory and delusional experiences, may also be affected by birth season. In the present study, we assessed the season of birth effect on the prevalence of PLEs using data from the cross-sectional survey of 19,436 Japanese adolescents. As a result, significant excess of winter births was observed in the prevalence of PLEs, accompanied by a decreased proportion of summer births. The odds ratios for the prevalence of PLEs were estimated to be 1.11, which was on the same order with those for the development of schizophrenia in the previous meta-analytic studies. To our knowledge, this is the first to show the seasonality of birth in the prevalence of PLEs and implicate the winter birth effect on subclinical stage of schizophrenia.

Keywords Schizophrenia · Winter birth · Summer birth · Hallucination · Delusion

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Introduction

A number of studies have investigated seasonality of birth in schizophrenia. Most of the studies have consistently observed an excess of winter births, often associated with a decreased summer births [1–3]. The rate of the increase of winter births was around 5–15 %, compared with the expected number of birth during the season, in most of the Northern Hemisphere [1]. The odds/relative risk ratios of winter births for the development of schizophrenia have been estimated in the order of 1.10 [1–3]. Various hypotheses to explain the reason for the seasonality have been discussed, including meteorological variables, infections, maternal hormones, sperm quality, nutrition and external toxins, although the discussion has not reached conclusion [4].

Psychotic-like experiences (PLEs) are subclinical hallucinatory and delusional experiences, occurring not only in psychotic patients but also in a portion of the general population [5, 6]. Recent studies have suggested that PLEs also occur in children and adolescents [7–9], and a continuum between PLEs in childhood and schizophrenia spectrum disorder in adulthood was demonstrated [10]. Although the predictive validity of PLEs for psychotic

disorder remains to be further studied, especially in case of those assessed by self-rating questionnaires [11], it may be worth investigating this phenomenon to elucidate the etiopathological mechanisms of schizophrenia and establish strategies for its prevention.

PLEs share an extensive range of risk factors with schizophrenia [12], while an association with winter–spring birth has failed to be shown [13]. Considering the previous study [13] used a total of 2,232 subjects, we may expect to detect the significant effect of birth season using larger amount of subjects. In the present study, we assessed the seasonality of birth effect on the prevalence of PLEs using data from the cross-sectional survey of 19,436 Japanese junior high and high school students.

Subjects and methods

Subjects

We used data from the cross-sectional survey of psychopathologies conducted from 2008 to 2009 in Kochi and Mie prefectures, Japan. Both prefectures are located in the mid to west part of Japan and approximately 300 km apart from each other, including both urban and rural areas (populations are approximately 750,000 and 1,800,000 for Kochi and Mie, respectively). In this survey, data were collected from students from 45 public junior high schools (7th–9th grade) and 28 senior high schools (10th–12th grade). Most of the schools in the middle areas of the two prefectures agreed to cooperate, and all of the schools were public. The total number of the current students of those high schools was 19,436 at the survey, and all of them were ethnically Japanese. Details of the procedure were described elsewhere [14]. We complied with Japan's Ethical Guidelines for Epidemiological Research, and the study was approved by the ethics committees of the Tokyo Institute of Psychiatry, the Mie University School of Medicine, and the Kochi Medical School.

Measures

PLEs were assessed by self-rating questionnaires using four items adopted from the schizophrenia section of the Diagnostic Interview Schedule for Children (DISC-C) [15]. These items were previously used in a birth cohort study and good predictors of schizophrenia spectrum disorder in adulthood [10]. The items were (1) "Some people believe that their thoughts can be read. Have other people ever read your thoughts?" (thoughts read); (2) "Have you ever had messages sent especially to you through the television or radio?" (special messages); (3) "Have you ever thought that people are following you or spying on you?" (spied upon); and (4) "Have you ever heard voices that other people cannot hear?" (heard voices), with a choice of three responses, 'no', 'yes, likely', or 'yes, definitely'. We defined 'yes, definitely' as the presence of a hallucinatory and delusional experience and 'no' or 'yes, likely' as no experience.

Statistical analysis

First, we defined winter and summer months according to the ambient temperatures (Supplementary Table 1) [16]. Winter months was defined as November to March, the average lowest temperature in the past 20 years of which was lower than 10 °C. Summer months was defined as July to September that of which was higher than 20 °C. April to June and October were treated as other months. We then assessed the seasonality of birth effect on the prevalence of PLEs using the Cochran–Armitage test for trend, i.e., the ordinal variables were allocated to winter, other, and summer months, and the linearity between the variable and the prevalence of the experience of at least one type of PLEs, "heard voice", or "spied upon" was tested. "Heard voice" and "spied upon" were analyzed separately on the basis of two reasons: one is that they may be considered as continua of delusion and auditory hallucination, typical positive symptoms of schizophrenia [6]. The other is that when using a self-report questionnaire, the sensitivity and specificity of these two items were among the highest to screen PLEs in adolescents in the previous study [17]. Last, we estimated the odds ratios of winter/summer births for the prevalence of PLEs using Chi-square test. The prevalence of the PLEs, "heard voice", or "spied upon" was compared in winter versus summer and other months, or summer versus winter and other months in all and divided subjects by gender, age (junior/senior high school), and survey area.

Results

Out of 19,436 students of the 45 junior and 28 senior high schools, 798 students (4.1 %) were absent on the days of the survey, and 388 students (2.0 %) did not agree to participate in the study. Thus, the total of 18,250 students (93.9 %) answered the questionnaire. Out of 18,250 subjects, 548 were excluded due to missing data for PLEs. Consequently, 17,702 subjects [8,747 males and 8,955 females, age = 15.2 ± 1.7 years (mean ± SD.)] were analyzed.

The prevalence of the four PLEs was as follows: "thoughts read" was observed in 205 subjects (1.2 %), "special messages" in 131 (0.7 %), "spied upon" in 1,141 (6.4 %), and "heard voices" in 1,715 (9.7 %) (the distributions by birth months are shown in Supplementary

Fig. 1). The experience of at least one type of PLEs was reported by 2,540 (14.3 %); 575 students (3.2 %) experienced two or more symptoms of PLEs.

Figure 1 summarizes the prevalence of PLEs according to the birth seasons. A significant association between the birth seasons and the experience of at least one type of PLEs or "heard voice" was observed ($\chi^2 = 4.24$ and 5.54, $df = 1$, $p = 0.022$ and 0.019, respectively).

As shown in Table 1, the odds ratio of winter birth excess was statistically significant in the experience of at least one type of PLEs and "heard voice" (OR = 1.11 and 1.11, 95 % CI = 1.02–1.21 and 1.00–1.23, $p = 0.016$ and 0.042, respectively). That of summer birth deficit was statistically significant in "heard voice" (OR = 0.85, 95 % CI = 0.79–0.99, $p = 0.041$). After dividing the subjects by gender, the odds ratios of winter birth excess and summer birth deficit were statistically significant in the experience of at least one type of PLEs in females (OR = 1.13 and 0.88, 95 % CI = 1.01–1.27 and 0.77–1.00, $p = 0.030$ and 0.048, respectively), while not in males (Supplementary Table 2). With respect to age, the junior high school students showed the statistically significant level of odds ratios for winter birth excess in the experience of at least one type of PLEs and "heard voice" (OR = 1.14 and 1.20, 95 % CI = 1.02–1.29 and 1.04–1.37, $p = 0.026$ and 0.010, respectively)

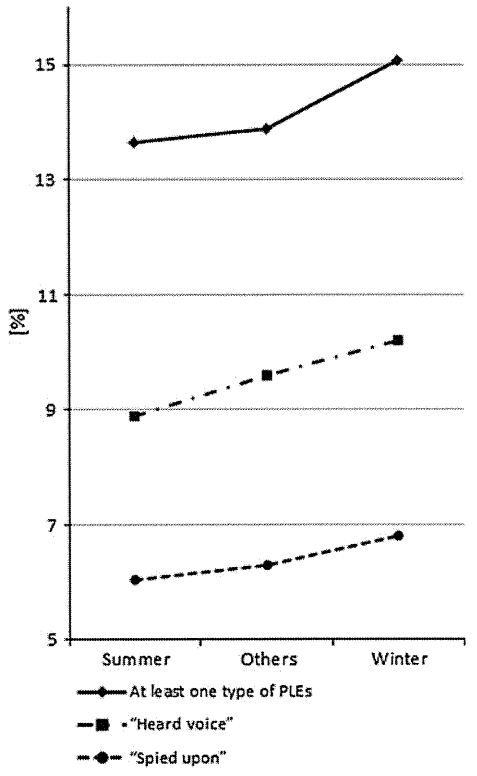

Fig. 1 Prevalence of PLEs according to the birth seasons: summer (July–September), others (April–June and October), and winter (November–March)

Table 1 The odds ratios of winter/summer births for the prevalence of PLEs

	At least one type of PLEs	"Heard voice"	"Spied upon"
Winter	1.11 (1.02–1.21)**	1.11 (1.00–1.23)*	1.11 (0.98–1.25)
Summer	0.93 (0.84–1.02)	0.85 (0.79–0.99)*	0.91 (0.79–1.05)

Odds ratios were calculated by comparing winter versus summer and other months, or summer versus winter and other months (described with 95 % CI in the brackets)

* $p < 0.05$

** $p < 0.02$

(Supplementary Table 2). After dividing the subjects by survey area, the subjects in Mie prefecture showed the statistically significant level of odds ratios for winter birth excess in the experience of at least one type of PLEs, "heard voice", and "spied upon" (OR = 1.31, 1.37 and 1.27, 95 % CI = 1.13–1.54, 1.14–1.64, and 1.02–1.58, $p = 0.00054$, 0.00073 and 0.031, respectively). The Mie subjects also showed the statistically significant level of odds ratio for summer birth deficit in the experience of "heard voice" (OR = 0.78, 95 % CI = 0.63–0.97, $p = 0.025$). In the Kochi subjects, the effect did not reach statistical significance (Supplementary Table 2).

Discussion

The present results showed a significant excess of winter births in the prevalence of PLEs in the Japanese adolescence, accompanied by a decreased proportion of summer births especially in "heard voice". The odds ratios for the prevalence of PLEs were estimated to be 1.11, which was on the same order with those for the development of schizophrenia in the previous meta-analytic studies [1–3]. This may be the first study to show the seasonality of birth in the prevalence of PLEs and suggest the winter birth effect on subclinical stage of schizophrenia.

The present subjects derived from Kochi and Mie prefectures, having mid to small size of population and located within the not far distance in the mid to west part of Japan. All of the recruited schools were public and distributed in the middle areas of the two prefectures, including urban and rural areas. Therefore, it is unlikely that the data of the subjects are significantly deviated from that of the general population of Japan in this generation. In the analysis after dividing the subjects by gender, age (junior/senior high school), and survey area, female, junior high school, and Mie subjects showed the statistically significant odds ratio of winter birth excess and/or summer birth deficit, while the similar non-significant tendencies were also observed in the other subgroups.

Until now, Polanczyk et al. [13] is the only study which investigated the season of birth effect on PLEs, to our knowledge. In their study using 2,232 British children of age 12 years, the odds ratio of winter–spring birth for the presence of PLEs was 1.3 (95 % CI = 0.8–1.9), while the statistical level was not significant (adjusted $p = 0.28$, unadjusted p by Chi-square test = 0.18).The present study, using larger number of adolescent subjects ($n = 17{,}702$), clearly showed the significant association between winter birth and PLEs. The definition of summer/winter seasons seems to be reliable because we defined them on the basis of the meteorological data and they were consistent with the conventional definition consequently. Considering share of an extensive range of risk factors between PLEs and schizophrenia [12], our findings may further support construct validity between the clinical and subclinical phenotypes of schizophrenia. The non-significant relationship with winter–spring birth in the previous study [13] may result from the lack of statistical power.

Several limitations may be considered before interpreting the present results. First, PLEs in the present study were assessed by self-rating questionnaires. The validity of self-reported PLEs has not been fully established; therefore, self-reported PLEs might not be equated with that in the original conceptualization [18]. Actually, PLEs were assessed by structured interviews by a child psychiatrist in the longitudinal study, which showed a continuum between PLEs in childhood and schizophrenia spectrum disorder in adulthood [10]. In that study [10], the prevalence of definite PLEs (1.6 %) was significantly lower than that in the present study (14.3 %), while some interview-based studies did not show very low prevalence (for instance, 6.6 % in Kelleher et al. [19]). Second, the clinical relevance of PLEs in childhood and their predictive validity for later development of psychosis and other mental disorders remains to be further studied [11]. While we found PLEs might be associated with suicidal risk and violent behaviors in the same cross-sectional survey data [20, 21], longitudinal studies may be needed to understand the characteristics of the subjects with PLEs. Third, we did not take into consideration the confounding effect of genetic or other environmental factors, including social class, urban birth, and obstetric complications [12]. It may be also interesting to analyze combined effect of the seasonality of birth and these other factors on PLEs because winter birth effect is small. Forth, we could not obtain answers from absent students. Poor mental health status and psychopathology may be more prevalent among frequent or long-term absentees.

In conclusion, PLEs, subclinical correlates of schizophrenia, may also be affected by birth season. Further investigation of this phenomenon may be recommended to elucidate the still unknown etiopathological mechanisms of schizophrenia and establish strategies for its prevention.

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Conflict of interest The authors declare that they have no conflict of interest.

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Psychoeducation for major depressive disorders: A randomised controlled trial

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ABSTRACT

Various psychological therapies have been shown to be effective for the treatment of mood disorders. Among them, family psychoeducation has demonstrated efficacy in reducing symptom severity and extending the time to relapse. We tested the efficacy of adding psychoeducation focussed on how to deal with the family's expressed emotion to treatment as usual (TAU) to prevent relapse among patients with remitted major depression. A total of 34 patients with major depressive disorders in full or partial remission were randomised to receive either group psychoeducation over six sessions, each consisting of a didactic lecture and group problem-solving ($n=19$), plus TAU or TAU alone ($n=15$). The primary outcome was relapse by *Diagnostic and Statistical Manual of Mental Disorders* fourth edition (DSM–IV) criteria. Masked raters administered the Hamilton Rating Scale for Depression-17 (HRSD-17). As many as 18 patients in the intervention group and 14 patients in the control group completed the study. Time to relapse was significantly longer in the intervention group than in the control group, with a risk ratio (RR) of relapse by 9 months of 0.12. At 9 months, there was a significantly greater decrease in the HRSD-17 score in the intervention group than in the control group. We demonstrated the effectiveness of patient psychoeducation on the course and outcome of major depressive disorders.

1. Introduction

Psychoeducation has demonstrated effectiveness for patients with depression as a first step in the treatment protocol in the NICE guidelines (National Institute for Health and Clinical Excellence, 2009), especially when used together with medication. Psychoeducational approaches to patients with schizophrenia and their families have developed partly based on studies of expressed emotion (EE) in the family (Brown et al., 1972; Vaughn and Leff, 1976). High-EE status in the family has been shown to be a risk factor for relapses of schizophrenia (Bebbington and Kuipers, 1994). Since 1982, studies on family intervention using EE as a target have shown the effects of psychoeducational family intervention for preventing relapses (Falloon et al., 1982; Tarrier et al., 1988; Shimodera et al., 2000). There have been a variety of psychological therapies demonstrated to be effective for the treatment of mood disorders (Hollon and Ponniah, 2010). Among them, psychoeducation is widely accepted as it fits very well with the medical model of illness by being a clinically focussed, commonsense-based intervention (Colom, 2011). Moreover, it is relatively simple and can be administered by therapists of various disciplines without extensive training.

Most of the research on psychoeducation for patients with mood disorders has been conducted with bipolar disorders. Colom and his colleagues (2003) investigated the effects of group psychoeducation for those with bipolar I and II disorders on the course of the disorders and showed that group psychoeducation significantly reduced the number of relapsed patients and the number of recurrences per patient. Colom and his colleagues (2009) also explored the efficacy of group psychoeducation for those with bipolar II disorders only and showed that psychoeducation plus medication significantly decreased the number of episodes and days spent in mood episodes and increased levels of functioning. Research has demonstrated the effects of family psychoeducation on the course of bipolar disorders. Compared to the control group, the family psychoeducation group showed less experience of any mood recurrence and longer relapse-free intervals (Miklowitz et al., 2003). Psychoeducation for patient–companion dyads has also been

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applied and has shown its effects on the course of bipolar disorders by reducing the number of relapses and the time to relapse (D'Souza et al., 2010). In the case of major depressive disorder (MDD), interpersonal therapy, cognitive behavioural therapy and behavioural therapy have vast empirical support through many randomised controlled trials demonstrating their efficacy (APA, 2004). The mainstream psychoeducational intervention for patients with depression is the 'Coping with Depression' (CWD) course, which is a cognitive behavioural intervention that treats and prevents depression in many target populations by providing them with instructions on how to cope with their psychological symptoms themselves (Lewinsohn (1975); Cuijpers et al., 2009). However, most of the studies using CWD are on complex target groups because of its flexibility, leading to low mean effect sizes (Cuijpers et al., 2009). The intervention itself is complex and requires eight to 16 sessions. Still, group psychoeducation for MDD can be effective (Colom, 2011). Donker et al. did a meta-analysis of psychoeducation for depression and anxiety (Donker et al., 2009). This meta-analysis revealed that brief passive psychoeducational interventions for depression and psychological distress can reduce symptoms (Donker et al., 2009). However, all the above-referenced psychoeducations are focussed on how to cope with their symptoms and none of them tried to focus on how to cope with their over-complicated relationship due to depression.

There have also been a number of reports describing an association between EE and relapse of depression (Hooley et al., 1986; Okasha et al., 1994; Mino et al., 2000, 2001). Our prospective study suggested that the association of EE with relapse might be even stronger in depression than in schizophrenia (Mino et al., 2001). In fact, we conducted family psychoeducation which sets a goal of reducing the family's EE for members with major depression and found that the time to relapse was much longer in the intervention group than in the control group (Shimazu et al., 2011). The family psychoeducation programme tested was simple and consisted of only four sessions of didactic lectures and group problem-solving exercises (Shimazu et al., 2011). Inspired by these encouraging results, we planned to provide persons with MDDs with a similar frame of psychoeducation without their family and to examine its influence on the course and outcome of the illness. Thus, the aim of this study was to test for patients with MDDs the effectiveness of simple psychoeducation which is focussed on how to cope with family members and colleagues and superiors at the workplace in a randomised controlled design.

2. Methods

2.1. Subjects

The subjects were patients who met the following eligibility criteria. The inclusion criteria were:

a) age between 20 and 70;
b) diagnosis of MDD in (partial) remission according to the *Diagnostic and Statistical Manual of Mental Disorders* fourth edition (DSM-IV) (APA, 2000);
c) not having undergone electroconvulsive therapy (ECT) or not having ECT already planned for the index episode; and
d) a Mini-Mental State Examination (Folstein et al., 1975) score of 24 or higher when patients are over 60.

The diagnostic assessments were done with Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The validity of the Japanese version of the MINI is already confirmed by Otsubo et al. (2005). Patients were excluded if they were suspected of having experienced a hypomanic/manic episode in the past, were diagnosed as having Axis II disorders or had co-morbid severe physical illness. Participants were recruited at the two affiliated hospitals of Kochi Medical School, Atago Hospital and Fujito Hospital in Japan, between July 2007 and January 2008. They were screened with the Mini-Mental State Examination (Folstein et al., 1975) when their age was over 60 and those with a score of 23 or lower were excluded since they were suspected of having possible dementia. Patients suspected of having organic disease were examined by head magnetic resonance imaging and those diagnosed with organic disease were excluded.

2.2. Procedures

We recruited patients from our practice who agreed to participate in our investigation.

The patients were assessed for eligibility using the criteria described before in Section 2.1 Subjects. The patients who satisfied the eligibility criteria received written informed consent to participate after full disclosure of the purpose and procedures of the study. After the agreement, the participants were randomly allocated to intervention and control groups. We used a straightforward random sequence without stratification or block as generated by use of a random number table. The random allocation list was centrally kept by a research assistant and the allocation was conveyed to the investigators and clinicians only after the participant was registered. Both the intervention and control groups were instructed not to mention whether or not they were receiving psychoeducation to their treating psychiatrists or to those performing psychiatric assessment. The control group received treatment as usual (TAU) while the intervention group received psychoeducation in addition. The details are described in Section 2.3. Nine months after finishing the intervention, they were analysed for the prevalence of relapse.

Ethical approval was obtained from the ethics committees at Kochi Medical School.

2.3. Psychoeducational sessions

Group psychoeducation was administered to the patients for six sessions that were held on a weekly basis. Each group consisted of between two and six patients, depending on the patient accrual and to minimise the waiting time. Each session lasted for about 1.5 h: the first 20–30 min were used for a didactic lecture and were followed by group discussions using problem-solving techniques.

The topics of the didactic parts included 'Patient recognition of depression and its consequences', 'Causes and risk factors', 'Signs and symptoms', 'Drug treatment', 'Side effects of antidepressants' and 'Course/outcome and review of the sessions'. As educational materials, we developed a textbook describing depression and its treatment and videos illustrating the patients' experiences, depressive symptoms and treatment.

In the group meeting, participants were encouraged to raise questions of any kind that they wanted to know or solve. There were a variety of questions raised: how they would inform the boss of their absence, how they should respond to family critical attitudes or emotional overinvolvement, how they could discuss trivial-looking family matters with the doctor in charge, how they could distinguish between mental disorder and character and so on. We focussed on how to cope with family members and the boss at the workplace, prompting use of the problem-solving techniques among the participants. We did not use psychotherapeutic techniques and homework tasks in our sessions.

The staff consisted of one psychiatrist, one clinical psychologist and a clerk. The psychiatrist provided all the lectures and led the group meetings supported by the clinical psychologist.

2.4. Treatment as usual

All the patients received outpatient treatment given by psychiatrists who were different from those administering psychoeducation, performing the psychometric assessments or judging relapse. This TAU consisted of clinical management including assessment of the psychiatric symptoms and subsequent prescription of antidepressant(s) once every 2 weeks. The duration of a clinical visit was about 15 min. All the patients were asked not to undertake any formal psychotherapy during the trial.

2.5. Assessment of psychiatric symptoms and function

When the treating psychiatrists suspected relapse, the patient was seen by an independent psychiatrist (HF), blind to the group assignment, to make a final judgement about whether a relapse had occurred.

To assess the severity of depressive symptoms, we administered the 17-item Hamilton Rating Scale for Depression (HRSD-17), which is observer-rated instrument designed to assess depressive symptoms over the previous week (Hamilton, 1967), and the Beck Depression Inventory-Second Edition (BDI-II), which is a 21-item, self-report measure of depressive symptoms using a 0–3 scale (range, 0–63) (Beck et al., 1961), at baseline, after the last session of psychoeducation in the case of the intervention group, at any point when a relapse was suspected and after 9 months. We also administered the Clinical Global Impression (CGI, Guy, 2000) severity score at baseline and after 9 months, and the CGI improvement score after 9 months. In addition, the Global Assessment of Functioning (GAF, APA, 2000) was rated at baseline and after 9 months. All the observer-rated instruments including HRSD-17, CGI and GAF were administered

by an independent psychiatrist (IM), who was different from those administering the treatment or judging relapse and who was also kept blind to the group assignment of the patients. Relapse was declared when the diagnostic threshold for a major depressive episode as specified in DSM-IV was met according to the interview by this independent psychiatrist. Remission was defined as an HRSD score of 6 or lower (Shimazu et al., 2011). We defined the state of partial remission according to DSM- IV.

2.6. Statistical analysis

Statistical Package for the Social Sciences (SPSS) for Windows version 18.0 was used for statistical analysis. Where data were continuous, parametric analysis such as the unpaired *t*-test was employed and where data were categorical, non-parametric analysis such as the chi-squared test/Fisher exact test was used. In order to compare the time to relapse, we used Kaplan–Meier survival analysis and Cox proportional hazard analysis to control for possible confounders. We showed the results of the intention-to-treat sample for these survival analyses. The 'end' point HRSD-17, BDI-II, CGI severity and GAF scores were compared between the intervention and control groups among the completers.

3. Results

Of the 34 patients randomly allocated to the intervention and control groups, one patient in the intervention group and one patient in the control group withdrew their consent before actually entering the study, resulting in 32 patients who entered the study, with 18 in the intervention group and 14 in the control group. During the study period, one patient in the intervention group dropped out and four patients in the control group changed hospitals. Follow-up data at 9 months for these five patients were not available, but we will focus on these 32 patients as our intention-to-treat sample, with the dropouts treated as censored cases as appropriate (Fig. 1).

The 32 participants who entered the study had a mean age of 42.8, mean duration of illness of 36.8 months, mean number of previous admissions of 0.3, mean HRSD-17 score of 11.4 and mean antidepressant dose of 125.7 mg (amitriptyline equivalent). In short, the majority of subjects were in their middle age and in a mildly depressive state. Comparison of the variables between the two groups showed no significant differences regarding demographic variables such as sex, age, education, living conditions (i.e., living with family/others or living alone), time from home to the hospital and clinical variables such as duration of illness, baseline HRSD-17, BDI-II, CGI severity or GAF scores (Table 1).

3.1. Adherence

Out of the 17 patients in the intervention group, 13 patients (76%) received the full six sessions, three received five sessions and one patient received only one session; she dropped out after finishing the first session but revisited the hospital and follow-up assessment was obtained.

3.2. Relapse

In the intention-to-treat analysis, relapse occurred in one patient (6%) in the intervention group and in five patients (36%) in the control group. The mean (standard deviation, S.D.) HRSD-17 and BDI-II scores at relapse were 25.0 (4.1) and 33.3 (6.1), respectively. Kaplan–Meier survival analysis showed that time to relapse was significantly longer in the intervention group than in the control group (Log-rank chi-squared=6.48, $df=1$, $P=0.011$) (Fig. 2). The median time to relapse was 274 days for the intervention group and 221 days for the control group. The crude risk ratio of relapse by 9 months was 0.12 (95% confidence interval (CI); 0.02–0.87, $P=0.015$), corresponding with a number needed to treat (NNT) of 3.2 (95%CI: 2.8–21.4).

In order to control for possible confounders, we conducted Cox proportional hazard analysis by entering sex, age, illness duration, baseline HRSD-17 score, baseline antidepressant dosage and intervention; only intervention emerged as a significant predictor of the time to relapse (hazard ratio, HR=0.091, 95%CI: 0.01–0.87, $P=0.038$) (Table 2). There were no significant differences between relapsers and non-relapsers in terms of other variables such as sex, age, education, living conditions, baseline HRSD-17, BDI-II scores and baseline dose of antidepressant(s).

3.3. Nine-month outcome

Nine-month outcomes were examined among the 27 patients who could be followed up. Follow-up HRSD-17, BDI-II, CGI severity and GAF were compared between the intervention and control groups to evaluate the effects of psychoeducation at 9 months using analysis of covariance (ANCOVA) with respective baseline scores as a covariate (Table 3). All the HRSD-17, the BDI-II, the CGI severity and the GAF scores were statistically significantly better in the intervention group than in the control group while controlling for their respective baseline scores. The CGI-improvement score was also significantly better in the psychoeducation group.

Sensitivity analyses were conducted by substituting the missing 9-month follow-up data for HRSD-17, BDI-II, CGI severity and GAF by their baseline values. Again, all the scores were significantly better in the intervention group than the control group (Table 3).

The rate of remitted patients in the intervention group was 10 out of 17 (58.8%) and that in the control group was two out of 10 (20.0%), indicating no significant difference between the two groups (Fisher's exact test; $P=0.110$).

3.4. Drug treatment variables

Among the completers, the baseline dose of antidepressant tended to be higher in the control group but was not significantly different between the intervention and the control groups (mean (S.D.) amitriptyline equivalent dose of 107.5 (52.8) vs. 134.0 (71.5) mg; $t=1.89$, $P=0.072$). Entering this variable in the Cox proportional hazard analysis, however, did not change the results. Neither were the types of antidepressants (i.e., newer-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) vs. older-generation antidepressants including tricyclic antidepressants (TCAs)) significantly different between the two groups.

At 9 months, the mean (S.D.) dose of antidepressant in the intervention group was 102.7 (59.2) mg and that in the control group 124.0 (57.1) mg, showing again no difference between the groups ($F=0.079$, $P=0.78$).

4. Discussion

This study demonstrated that group psychoeducation consisting of six sessions was effective in treating MDDs and preventing relapses for up to 9 months of follow-up. Time to relapse was significantly longer in the psychoeducation group and the 9-month outcomes in depressive symptomatology and function were better in the intervention group than in the control group. These findings were not related to the drug treatment.

There have been several studies demonstrating the effectiveness of psychoeducation on the course and outcome of mood disorders but our programme is distinct from the pre-existing ones in the following aspects. Our programme targets patients with unipolar depression, whereas many of the pre-existing ones have included patients suffering from bipolar disorders (Colom et al., 2003; Colom et al., 2009). Ours involves patients only, whereas in others either only family members received psychoeducation (Miklowitz et al., 2000; Reinares et al., 2008; Shimazu et al., 2011) or both the patients

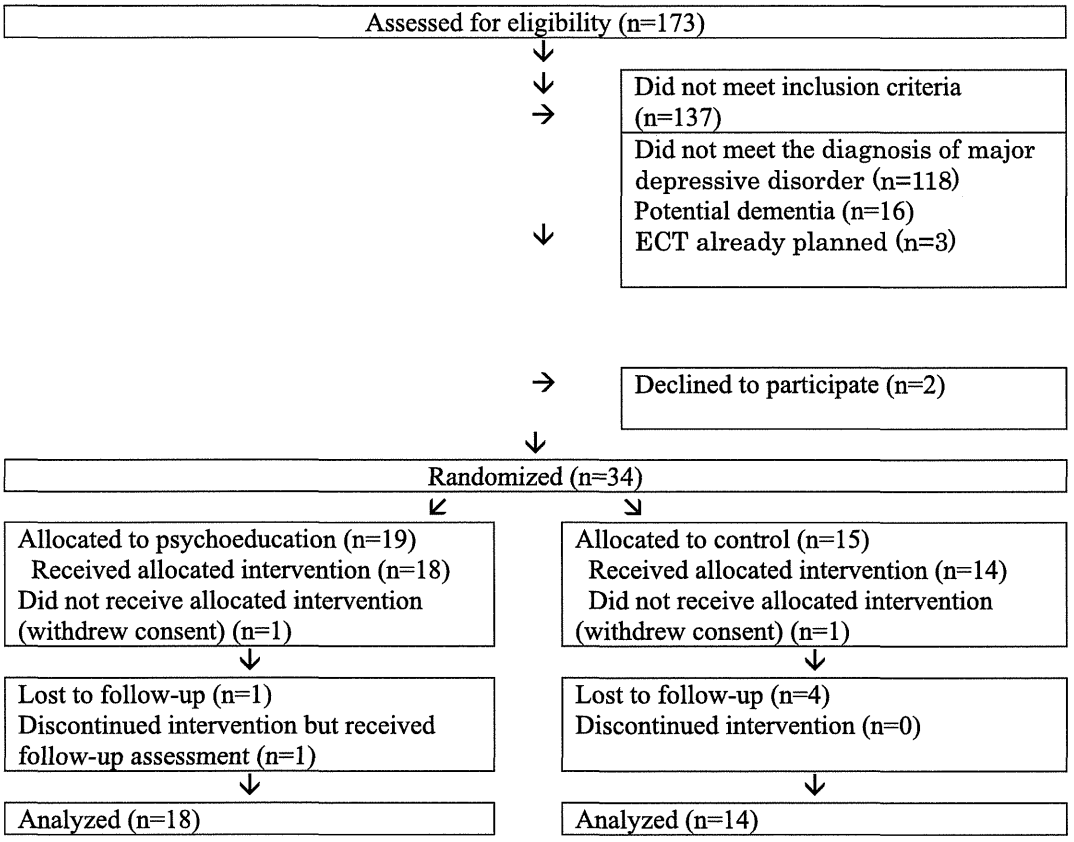

Fig. 1. Flow of participants through the trial.

Table 1
Baseline characteristics of the experimental and control groups.

	Intervention ($N=18$)	Control ($N=14$)	
Gender: Male/Female	6/12	8/6	ns (chi-squared $p=0.178$)
Age (years): Mean(SD)	44.8 (12.0)	40.3 (9.3)	ns (t test $p=0.251$)
Time from home to hospital (minutes); Mean(SD)	26.0 (13.0)	31.3 (24.4)	ns (t test $p=0.437$)
Education; n(%)			
Graduation from junior high school	1 (6)	0 (0)	ns (chi-squared $p=0.364$)
Graduation from senior high school	4 (22)	7 (50)	
Graduation from junior college	7 (39)	4 (29)	
Graduation from university	6 (33)	3 (21)	
Living conditions; n			
Lives with family or others/Lives alone	15/2	11/2	ns (Fisher $p=1.000$)
Duration of illness (m): Mean(SD)	37.3 (45.2)	35.9 (24.2)	ns (t test $p=0.921$)
Number of admission: Mean (SD)	0.2 (0.5)	0.4 (0.6)	ns (t test $p=0.226$)
HRDS: Mean(SD)	12.4 (5.5)	10.0 (5.3)	ns (t test $p=0.336$)
BDI-II: Mean(SD)	24.1 (12.0)	19.9 (9.4)	ns (t test $p=0.305$)
CGI severity: Mean(SD)	3.3 (0.6)	2.9 (0.8)	ns (t test $p=0.057$)
GAF: Mean(SD)	56.3 (11.2)	60.6 (13.0)	ns (t test $p=0.323$)
Dose of antidepressant(s) (mg): Mean(SD) (amitryptiline equivalent)	108.1 (51.2)	148.3 (71.0)	ns (t test $p=0.072$)

and their companions had to participate in the psychoeducation sessions (D'Souza et al., 2010). Another very well-known program, CWD, is a fully structured cognitive-behavioural psychoeducational programme, which targets patients with unipolar depression but requires eight to 16 sessions. Our brief psychoeducation intervention, which aims to reduce the stress from the family environment and the workplace by providing the patients with knowledge about depression and its treatment and with skills to cope with such stresses, demonstrated effectiveness as well.

There are several factors that can explain the effectiveness of patient psychoeducation for major depression. One possibility is being associated with medication adherence. This modifier was confirmed in the bipolar disorder study on a dyadic group-based psychoeducation programme (D'Souza et al., 2010). However, in our sample, adherence to the antidepressant treatment was not different between the intervention and control groups. Another possible explanation is the effect of the psychoeducation. The identification of the warning signs and a consequent early intervention might have been more effectively accomplished in the educated group. This mechanism was demonstrated in the study of Perry et al. (1999) who taught the patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. We administered the questionnaire on the knowledge about depressive disorders at baseline to the patients; well-recognised signs of depression included insomnia, depressive mood and restlessness, while many vegetative symptoms and forgetfulness were not recognised as a part of depressive

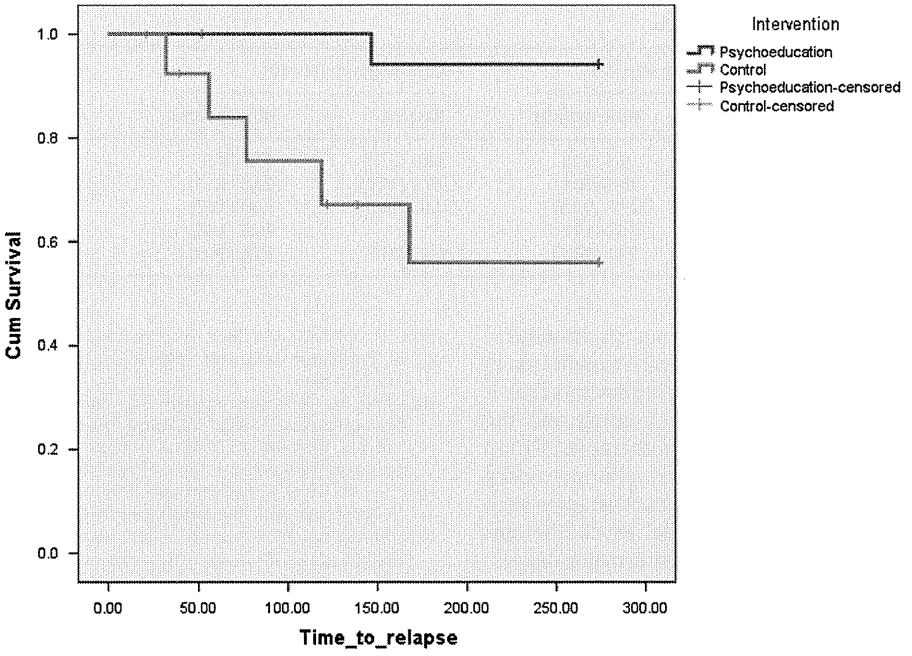

Fig. 2. Time to relapse by treatment group.

Table 2
Cox proportional hazard analysis adjusting for baseline variables.

	B	SE	p	Exp(B)	95% CI
Intervention	−2.39	1.15	0.038	0.091	0.010–0.87
Gender	−0.69	0.92	0.45	0.50	0.83–3.03
Age	0.01	0.05	0.85	1.01	0.92–1.11
Duration of illness	−0.03	0.03	0.28	0.97	0.92–1.03
Antidepressant dosage	−0.01	0.01	0.50	0.99	0.98–1.01
Baseline HRSD	−0.04	0.11	0.73	0.96	0.77–1.2

symptoms. Unfortunately, we did not re-administer the questionnaire at the end of the study, and we cannot know whether this educational factor was at play among our patients (data not shown). The patients in our intervention group may or may not have recognised more of their early signs/symptoms of relapse leading to successful coping with the situation.

Although information-giving methods are common, the techniques of psychoeducation seem to be different among the studies. Comparing psychoeducation and problem-solving groups, Dowrick et al. (2000) used relaxation, positive thinking, pleasant activities and social skills as psychoeducative methods. Colom et al. (2003; 2009) used communication-skills training and problem-solving training in addition to giving information ranging from the nature of the illness to issues of treatment and legal/social resources. Further, D'Souza et al., 2010 used an illness management approach by empowering a trusted figure to intervene and Miklowitz et al. (2003) included relapse prevention strategies. Psychoeducation offered in this study consisted of two parts in every session. The first half was devoted to giving information and the second half to discussing the problems the patients were facing. We did not set any topic limits at the sessions. In addition, the number of participants was about four, which indicates a high staff/patient ratio. In our experience of family psychoeducation, the staff/patient ratio and total amount of time used for the sessions are instrumental to acquiring precise knowledge (Sota et al., 2008). In fact, the patients appeared very content with 'long intimate' talks with professionals. However, data for proving the nonspecific influence of our psychoeducation method on the outcome were not available from this study.

5. Limitations

Our study has some limitations. First, the majority of our subjects suffered from mild depression and were middle-aged. This patient profile is very popular in outpatient treatment settings in Japan. However, the generalisability of our findings to other types of depression and other types of patients may not be taken for granted. Second, the number of patients was small so that we may have missed some significant effect modifiers. For example, there may be some variables related to the outcome other than psychoeducation. Third, we fell short of examining important effect modifiers in the psychoeducation. The mechanism of psychoeducation should be examined in more detail with assessment tools longitudinally measuring the knowledge and behaviour of the participants. Fourth, our programme consisted of narrowly defined patient psychoeducation per se plus problem-solving-based techniques. The patients also enjoyed long and close contact with mental health professionals at a high staff/patient ratio. We could not separately examine which of these specific and nonspecific factors were responsible for the observed effectiveness. The present study was only able to answer the research question that it had set out to ask, namely, whether adding the psychoeducation package to TAU decreased relapse in comparison with TAU alone. A more detailed study design with more parallel control interventions such as an equal number and length of sessions by an equal number of staff, but with a psychoeducation control condition on the one hand and with a problem-solving exercise control condition on the other, would be necessary to tease out the contribution of these specific and nonspecific treatment components. Fifth, it must also be pointed out that we failed to check the integrity of the treatments delivered in this study. It is therefore possible to discuss what we intended to provide but impossible to compare the actual components of the treatments provided. The adherence of the therapists as well as the patients needs to be monitored and evaluated in future studies. Lastly, relapse was suspected by blinded, treating psychiatrists and was confirmed by another independent, blinded psychiatry in our study. We failed to administer structured diagnostic interviews to all the patients and we may have underestimated the relapse rates among both the intervention and the control arms.

Table 3
The treatment of data of the intervention and control groups.

	Intervention group (N=17)		Control group (N=10)		ANCOVA	Sensitivity analyses
	Baseline	Nine months	Baseline	Nine months	*p*	*p*
HRSD: Mean(SD)	12.4 (5.7)	6.5 (5.3)	10.6 (5.0)	15.0 (8.5)	0.002	0.004
BDI-II: Mean(SD)	23.9 (12.3)	10.4 (10.1)	19.0 (10.7)	21.8 (12.2)	0.008	0.002
CGI-severity: Mean(SD)	3.35 (0.61)	2.47 (0.94)	3.00 (0.67)	3.40 (1.07)	0.035	0.049
CGI-improvement: Mean (SD)	–	2.12 (1.11)	–	4.20 (1.48)	< 0.001	–
GAF: Mean(SD)	56.0 (11.4)	77.1 (12.4)	60.9 (11.7)	61.6 (18.0)	0.02	0.007

Despite these weaknesses, our method of group psychoeducation, which is simple and easily introduced, can benefit many patients with MDDs. Furthermore, it must be emphasised that it may well be more cost-effective both for the training and the provision of the treatment than individual psychotherapies. Group psychoeducation may be delivered not only as an adjunct to drug therapies but also in concert with individual psychotherapies such as cognitive-behaviour therapy and interpersonal psychotherapy. Further studies of psychoeducation in patients with major depression are warranted to replicate and extend the usefulness and effectiveness of this psychosocial treatment.

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RESEARCH ARTICLE Open Access

A greater number of somatic pain sites is associated with poor mental health in adolescents: a cross-sectional study

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Abstract

Background: Identifying indicators of poor mental health during adolescence is a significant public health issue. Previous studies which suggested an association between the number of somatic pains and depression have mainly focused on adults or have employed samples with a narrow age range. To date, results from previous studies have been inconsistent regarding the association between somatic pain and academic impairment. Therefore, the main aims of the present study were to 1) investigate the association between the number of somatic pain sites and poor mental health using a community sample of adolescents aged 12 to 18 years and employing a simple method of assessment, and 2) examine the association between the number of somatic pain sites and perceived academic impairment.

Methods: Data analysis was conducted using a large cross-sectional survey of adolescents in grades 7 to 12. The one-month prevalence rates for three sites of somatic pain including head, neck and shoulders, and abdomen were examined. Poor mental health was evaluated using the General Health Questionnaire, and perceived academic impairment was measured using a self-report questionnaire.

Results: A total of 18,104 adolescents participated in the survey. A greater number of pain sites was associated with poor mental health, and this association was consistent across age and gender. There was no difference in effect on mental health between any of the pain sites. Although there was an association between the number of somatic pain sites and perceived academic impairment, the results suggested that the association was mediated by poor mental health.

Conclusions: Simple reporting methods for assessing the number of pain sites may be a feasible indicator of poor mental health in adolescents. Professionals working with adolescents should consider the possibility of poor mental health, especially when students report multiple somatic pains.

Keywords: Number, Somatic pain site, Poor mental health, Adolescents, Males and females, Academic impairment

Background

Mental health problems are a serious public health concern, especially among adolescents. Moreover, depression is the leading cause of disease burden in young people aged 10–24 years [1], with suicide the second leading cause of death within this age group, accounting for approximately 6% of total deaths [2]. However, a survey conducted in Europe demonstrated that use of psychiatric services among young people was lower than among adults [3]. This may be due to the fact that young people with depression are reluctant to seek help from professionals [4]. Thus, it is important for professionals working with adolescents to detect signs of poor mental health in youth. For the purpose of early detection, sensitive and feasible indicators of poor mental health in adolescents are required.

One indicator of poor mental health is somatic pain. Previous studies have found that such pain is a common

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complaint among adolescents [5,6]. A survey employing a large sample from the Netherlands showed that approximately 54% of children and adolescents had experienced somatic pain within the previous 3 months [7]. This study also demonstrated an association between somatic pain and poor mental health, as well as physical discomfort caused by somatic pain. A recent study reported that abdominal pain was associated with depressive symptoms in schoolchildren [8], while an additional study demonstrated a correlation between low back pain and depression in adolescents [9]. In addition to studies investigating single sites of pain, several previous studies have simultaneously examined multiple sites of pain. Although a linear relationship between number of pain sites and level of depression has been suggested in a few previous studies using adolescent samples [10,11], those studies used samples with relatively narrow age ranges and took into account only frequently reported pains. Because complex questions and long-term recall are required to characterize pain in more detail, including its severity, frequency, and nature, we speculated that a simpler reporting of pain might be feasible as an indicator. Therefore, the present study employed a broad age range during adolescence and a simple report of somatic pain.

A previous study demonstrated that children with somatic pain had substantial impairment in their daily lives [12]. However, the association between somatic pain and academic impairment has not been thoroughly examined. Given that school is equivalent to "work" for adolescents, that association should be a focus of investigation. Additionally, results among previous studies regarding the association between academic impairment and somatic pain have been inconsistent [13,14]. Although a previous study found that students with chronic pain experienced a decline in academic grades [13], another study reported that the level of academic competence in adolescents with chronic pain was consistent with their intellectual ability [14]. Therefore, further study examining the link between academic impairment and somatic pain is warranted.

Thus, the objectives of the present study were to 1) investigate the association between the number of somatic pain sites and poor mental health in a large sample of adolescents with a broad age range using a simple method of assessment, and 2) examine the association between the number of pain sites and perceived academic impairment.

Methods

Study design, sample, and survey procedures

The present study employed a cross-sectional design and used a sample of adolescent students in public junior high schools (7th–9th grades) and public high schools (10th–12th grades). The survey was conducted between 2008 and 2009. Under Japanese law, junior high school education is compulsory, but high school education is not. The present study was approved by the ethics committees of the Tokyo Institute of Psychiatry, Mie University School of Medicine, and Kochi Medical School. This research was conducted in accordance with the Helsinki Declaration as revised in 1989.

The principal investigators of the study asked all the heads and administrators of public junior highs in the city of Tsu (population 280,000) and public junior high/high schools in Kochi prefecture (population 790,000) to participate in the survey. Subsequently, the administrators and heads of schools consulted with teachers and parents to obtain their consent to participate. Instructions and guidelines for the distribution and collection of the questionnaire packets were provided to the teachers in the participating schools. For each school, teachers distributed the questionnaires to students, along with envelopes to place their surveys in when completed. All student responses remained confidential and were handled anonymously. Furthermore, teachers explained that participation in the study was strictly voluntary and assured confidentiality. Teachers reported on the total number of students who participated on the day of the survey. The research team collected the sealed envelopes from each school.

Measures

The distributed questionnaire packets included the following items: 1) the Japanese version of the 12-item General Health Questionnaire (GHQ-12) [15]; 2) a list of three sites of somatic pain (head, neck and shoulder, and abdomen); 3) perceived academic competence; and 4) additional variables including demographic characteristics, sleeping time, history of substance use, and the experience of being bullied or being subjected to violence.

GHQ-12

The GHQ-12 is one of the most widely used self-report measures for assessing anxiety and depression [16]. It has been used and validated in younger samples as well as in adults [17]. Additionally, previous studies have established the validity and reliability of the Japanese version of the instrument [15]. A 4-point scale using binary scoring (0011) was used for the 12 GHQ items. Responses for each question were added together to form a total score, with a range between 0 (best possible) and 12 (worst possible). We defined individuals with a total GHQ-12 score ≥4 as having poor mental health, based on findings from previous studies [17,18].

Three sites of somatic pain

The one-month prevalence of somatic pain was assessed using a list of three main sites for pain experienced

including head, neck and shoulders, and abdomen. Participants were asked to mark all the sites where they had experienced pain in the previous month. The three sites for somatic pain were chosen based on previous reports of pain with the highest prevalence among adolescents. According to these studies, headache and abdominal pain are the two most prevalent somatic pains experienced during adolescence [6,10]. Based on prevalences reported in previous studies [6,10,19], neck and shoulder pain is the third most prevalent. Participants who marked a particular site for pain were considered to have pain at that site.

Perceived academic impairment

Perceived academic impairment was assessed using the following two questions: "Have you had difficulty concentrating on your studies recently?" "Do you feel frustrated with a recent decline in your academic performance?" The participants were asked to choose one response from the following four: "yes", "somewhat", "not really", and "no". The participants who selected "yes" were regarded as having a perceived academic impairment.

Additional variables

One-month prevalence of alcohol use and smoking were assessed using a yes/no response format. Lifetime prevalence of any drug use was assessed using the following question: "Have you ever used any drugs?" The participants selected one of the following four responses: "no", "only once", "twice", "more than three times". Those who indicated using at least once were identified as drug users. The experience of being bullied within the past year and violence from adult cohabitants within the previous month were assessed dichotomously. Sleeping time was assessed using the following question: "Approximately how many hours do you sleep every day?" Sleeping 7 hours or less was regarded as a short sleeping time. Previous reports have shown an association between somatic pain and sleep problems such as reduced sleep [20,21]. Demographic characteristics including age, gender, and school grade were also assessed.

Statistical analysis

One-month prevalence of somatic pains was calculated. Chi-square tests were performed to compare the prevalence of somatic pains between genders or school grades. The prevalence of each somatic pain was compared using the McNemar test. The parametric t-test was used to compare means of GHQ-12 total scores between genders or school grades.

Multivariable analysis using logistic regression modeling was performed in which the outcome of interest was poor mental health, and the exposure of interest was the number of pain sites. Variables found to have an association with both outcome and exposure were selected as possible confounders. The likelihood ratio test was performed to examine interaction between age, gender, and the number of pain sites. A similar analysis was conducted treating each pain site as the exposure of interest.

In addition, multivariable logistic regression analysis was conducted in which the outcome of interest was perceived academic impairment, and the exposure of interest was the number of pain sites. The first model included only age and gender as confounding variables. The second model included additional confounders based on findings from previous studies [20,22]. The third model included the total score for GHQ-12 to examine the effect of poor mental health on the association between somatic pains and perceived academic impairment.

Results

The schools that agreed to participate in this study were from the following areas in Japan: 13 out of 20 public junior high schools in the city of Tsu, and 32 out of 118 public junior high schools and 28 out of 36 public high schools in Kochi prefecture. Among the 19,436 students from the participating schools, 18,638 were approached at school (798 were absent), of whom 18,250 agreed to participate in the survey. From these 18,250 participants, 18,104 responses were analyzable (a total of 93.1% of students from all the schools). Of these 18,104 students, 49.7% were male, and 50.3% were female. Their age ranged from 12 to 18 years, with a mean age of 15.2 years (SD = 1.7 years).

The one-month prevalences of each type of somatic pain for each gender and school grade are presented in Table 1. For all three somatic pains, the prevalence was higher in females than in males ($p < 0.01$). One-month prevalences of headache and abdominal pain were higher than that of neck and shoulder pain ($p < 0.01$). Regarding differences among school grades, the prevalence of neck and shoulder pain was higher in high school students than in junior high school students ($p < 0.01$). The prevalence of headache and abdominal pain was comparable between junior high and high school students.

Mean total score for the GHQ-12 was significantly higher in females than in males ($p < 0.01$). Moreover, the mean total score for the GHQ-12 was higher in high school students than in junior high students ($p < 0.01$).

Stratified odds ratios for each age and gender group are presented in Table 2. According to the test for interaction, there was no interaction between age and number of pain sites or gender and number of pain sites ($p = 0.84$ and $p = 0.31$, respectively).

Table 1 One-month prevalence of somatic pains and the 12-item General Health Questionnaire (GHQ-12) scores by school grade

		Headaches		Neck and shoulder pain		Abdominal pain		GHQ-12 total score		Difficulty in concentrating on study		Frustration with poor academic performance	
	N	N	(%)	N	(%)	N	(%)	Mean	SD	N	(%)	N	(%)
Demographic characteristics													
Junior high school (7^{th}-9^{th})													
Males	4446	1273	(28.6)	509	(11.4)	1197	(26.9)	2.45	2.77	748	(17.0)	993	(22.6)
Females	4174	1807	(43.3)	951	(22.8)	1958	(46.9)	3.82	3.18	875	(21.1)	1185	(28.7)
Total	8620	3080	(35.7)	1460	(16.9)[a]	3155	(36.6)	3.11[b]	3.05	1623	(19.0)	2178	(25.5)
High school (10^{th} -12^{th})													
Males	4546	1215	(26.7)	630	(13.9)	1128	(24.8)	3.15	3.00	1004	(22.3)	1202	(26.6)
Females	4938	2123	(43.0)	1483	(30.0)	2066	(41.8)	4.62	3.19	1204	(24.5)	1433	(29.2)
Total	9484	3338	(35.2)	2113	(22.3)[a]	3194	(33.7)	3.92[b]	3.18	2208	(23.4)	2635	(28.0)
Total													
Males	8992	2488	(27.7)[c]	1139	(12.7)[c]	2325	(25.9)[c]	2.81[d]	2.91	1752	(19.6)	2195	(24.6)
Females	9112	3930	(43.1)[c]	2434	(26.7)[c]	4024	(44.2)[c]	4.25[d]	3.21	2079	(22.9)	2618	(29.0)
Total	18104	6418	(35.5)[e]	3573	(19.7)[e]	6349	(35.1)[e]	3.53	3.15	3831	(21.3)	4813	(26.8)

a: the prevalence of neck and shoulder pain was higher in high school students than in junior high school students ($p < 0.01$).
b: mean total score for the GHQ-12 was higher in high school students than in junior high school students ($p < 0.01$).
c: prevalence was higher in females than in males ($p < 0.01$).
d: mean total score for the GHQ-12 was higher in females than in males ($p < 0.01$).
e: the prevalence of headache and abdominal pain were higher than that of neck and shoulder pain (both $p < 0.01$).

The odds of poor mental health increased as the number of pain sites increased (Figure 1). A total of 76.2% of students who reported three pain sites had poor mental health, while less than one third of students without pain had poor mental health.

Table 2 Effect of the number of pain sites on mental health by age group and gender

	Total	1 pain site		2 pain sites		3 pain sites	
	N	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age (years)[a)]							
12	720	1.88	(1.20–2.95)	3.20	(1.88–5.46)	3.97	(1.82–8.67)
13	2937	1.92	(1.55–2.38)	3.71	(2.91–4.74)	5.88	(3.94–8.77)
14	3011	1.75	(1.42–2.14)	2.57	(2.03–3.25)	4.96	(3.40–7.24)
15	3060	1.60	(1.32–1.95)	3.00	(2.39–3.76)	5.45	(3.79–7.83)
16	3438	1.76	(1.47–2.10)	3.29	(2.64–4.10)	6.46	(4.43–9.41)
17	3096	2.07	(1.72–2.50)	2.87	(2.27–3.63)	5.04	(3.44–7.39)
18	1842	2.14	(1.67–2.76)	3.28	(2.43–4.42)	5.38	(3.29–8.79)
Gender[b)]							
Males	8992	1.84	(1.64–2.06)	3.02	(2.61–3.50)	4.23	(3.28–5.47)
Females	9112	1.87	(1.67–2.10)	3.16	(2.78–3.60)	6.28	(5.13–7.69)

a) odds ratio in comparison with those with no pain sites, adjusted for alcohol use, smoking, drug use, sleeping time, experience of being bullied and violence from parents, and gender.
b) odds ratio in comparison with those with no pain sites, adjusted for alcohol use, smoking, drug use, sleeping time, experience of being bullied and violence from parents, and age.

Each site of somatic pain alone increased the odds of having poor mental health (Table 3). Although the OR for neck and shoulder pain was slightly higher than for the other two pain sites, there was no significant difference among the ORs for the three pain sites. With respect to a combination of two different sites of pain, there was no significant difference in the ORs among the three different combinations.

Results showed that difficulty in concentrating on studies increased as the number of somatic pain sites increased (Table 4). However, after adjusting for GHQ-12 total score, there was no evidence of an association between the number of pain sites and difficulty in concentrating. This suggested that the effect of somatic pains on concentration when studying may have been mediated by poor mental health.

Similarly, frustration regarding a recent decline in academic performance increased as the number of pain sites increased (Table 4). As a result of multivariate logistic regression, a substantial decrease in odds ratio was observed after adjusting for GHQ-12 total score, which also suggested a mediating effect of poor mental health.

Discussion

The present study was one of the first using a large sample of adolescent students aged 12 to 18 years that showed a greater number of somatic pain sites associated with poor mental health. An important implication of the present

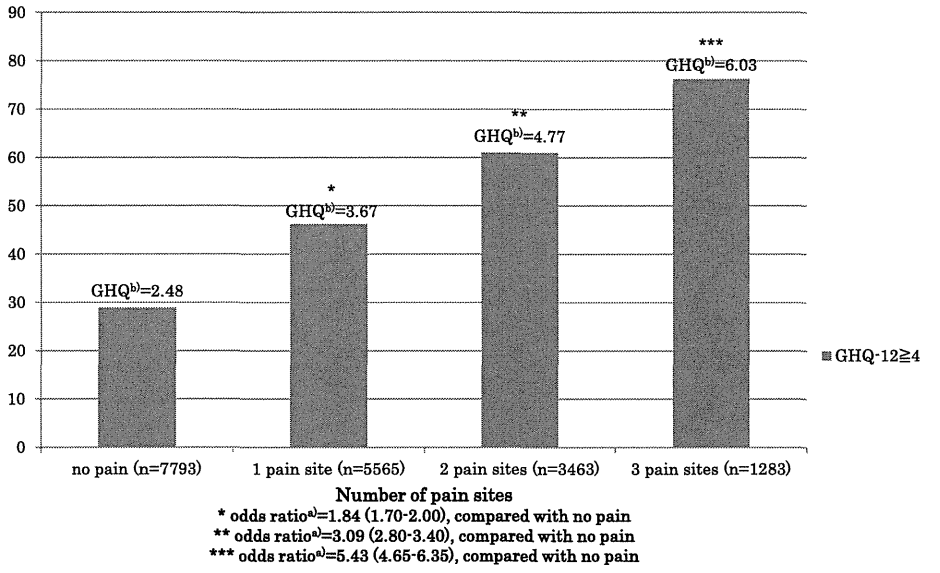

Figure 1 Association between number of pain sites and poor mental health.

study is that simple questions may be used to properly assess the three most prevalent somatic pains reported by this population. In turn, somatic pains may be feasible indicators of poor mental health in adolescents. Furthermore, the present findings suggest that the positive association between the number of pain sites and perceived academic impairment was mediated by poor mental health.

The present study did not restrict reports of pain to only those considered chronic or intense. Thus, a direct comparison with previous studies that examined chronic or frequent pain could not be made [6,7,10,19]. However, the prevalence of somatic pains in the present study was similar to that reported in previous studies. Additionally, a higher prevalence was found in females compared to males, which was in line with previous studies [7,10,19]. Moreover, a higher prevalence of somatic pains among older students was found, also consistent with previous research [7,19].

The mean total score of the GHQ-12 was similar to that found in a previous study (3.54, SD 3.04) conducted in Japan [17]. With regard to a mean difference in mental health between males and females, the present findings were consistent with past research that demonstrated a higher prevalence of emotional problems in females than in males [23]. In addition, in terms of school grade, the present study's findings correspond with a previous study reporting that somatic symptoms increase with age [23].

The present study revealed that the association between number of pain sites and poor mental health was consistent across males and females, as well as across a broad age range during adolescence. The observed association between a greater number of pain sites and poor mental health was consistent with previous studies [10]. However, because the present study employed a cross-sectional design, a causal relationship could not be determined. To date, a bidirectional relationship between somatic pain and poor mental health has been

Table 3 Association between site of pain and risk for poor mental health

		GHQ-12≧4		Odds ratio[a)]
	N	N	%	(95% Confidence Interval)
no pain	7793	2252	28.9	(reference)
headache only	2272	1015	44.7	1.80 (1.62-2.01)
neck and shoulder pain only	1000	505	50.5	1.97 (1.69-2.29)
abdominal pain only	2293	1049	45.7	1.84 (1.65-2.05)
headache and neck and shoulder pain	690	435	63.0	3.31 (2.75-3.97)
headache and abdominal pain	2173	1308	60.2	3.09 (2.76-3.47)
abdominal pain and neck and shoulder pain	600	369	61.5	2.93 (2.41-3.55)

a) odds ratio adjusted for age, gender, alcohol use, smoking, drug use, sleeping time, experience of being bullied and violence from parents.